CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
DIMETHIPIN

Chemical Code # 002159, Tolerance # 00406
SB 950 # 242
June 1, 2001

I. DATA GAP STATUS

Chronic/Onco Combined, rat	No data gap, no adverse effects
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effects
Reproduction, rat:	No data gap, no adverse effects
Teratology, rat:	Data gap, inadequate study, no adverse effects indicated[1]
Teratology, rabbit:	Data gap, study inadequate, no adverse effects indicated [1]
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	Data gap, inadequate studies, no adverse effects indicated[1]
DNA damage:	No data gap, no adverse effects
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.
[1] The studies in these areas are possibly upgradeable with submission of additional data.

All record numbers through 144268 and 900000+ and through volume 406-029 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T010601
Original by: J.S. Kishiyama and Gee, 6/1/01.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 029 144268 Goldenthal, E. I. "Two-Year Dietary Chronic Toxicity and Oncogenicity Study in Rats". (MPI Research, Laboratory ID 399-134, January 16, 1996.) Harvade® Technical, purity 98.5%, was administered for two years in the diet of Crl:CD® BR (VAF/plus) rats at concentrations of 0, 40, 1750, or 3500 ppm for 60 males/group and at 0, 40, 875, or 1750 ppm to 60 females/group. Mean doses were 0, 1.75, 77.6 and 161 mg/kg/day for males and 0, 2.18, 50.3 and 103 mg/kg/day for females. Ten/sex/group were sacrificed at 12 months. Hematology, clinical chemistry, and urinalysis were performed at 6, 12, 18 and 24 months, 10/sex/group. Ophthalmology was performed pretest and at 12 and 24 months. Survival was slightly reduced (65% of the control) for high dose females with 13/50 surviving compared with 20/50 for controls, excluding the intermediate sacrifice. Of the early deaths/sacrifices in high dose females, 11 were associated with chronic progressive nephropathy. Body weight was decreased for mid and high dose groups, both sexes, but food consumption was comparable. The kidney and liver were indicated as the primary target organs with increased incidence of kidney nephropathy and bile duct hyperplasia and biliary cysts in the mid and high doses, especially in females. In addition, increases in the incidence of hyperplasia of the duodenum and increased cholesterol levels were reported for mid and high dose groups. NOEL = 40 ppm. No adverse effect. ACCEPTABLE. (Kishiyama and Gee, 5/30/01).

** 006, 025 986746, 051259 Serota, D. G, R. D. Alsaker, K. K. Dawkins and W. Kundzins. "104-Week Chronic Toxicity Study in Rats N252 (Harvade Technical)." (Hazleton Laboratories America, Inc., Project No. 798-177, April 30, 1981.) N252 (Harvade Technical) considered 100% pure (lot D-10406) was admixed with the feed at concentrations of 0, 40, 200, or 1000 ppm and fed to 50 Sprague-Dawley rats/sex/group for 104 weeks and evaluated for chronic toxicity and carcinogenic potential. Body weight and bodyweight gain were reduced and liver organ weight increased for the high dose groups. Histopathological changes in the liver were of questionable toxicological significance. Cholesterol level was increased for mid and high dose groups. No adverse effects. NOEL = 40 ppm. Initially reviewed as unacceptable (no analysis of feed/test article, no rationale for dose selection). (J. Remsen, 7/1/85) Record 051259 contains the analysis of the diet, upgrading the study to ACCEPTABLE status with some minor deficiencies as noted in the initial review. (Gee, 5/29/01).

015 031936 Addendum to 986746 addressing pathology. No worksheet, (Remsen, 7/1/85)

CHRONIC TOXICITY, RAT

See combined chronic/onco, rat

CHRONIC TOXICITY, DOG

**** 005 986747** Jessup, D. C., Study director. "1-Year Dietary Toxicity Study in Dogs with N252." (International, Research and Development Corporation, Study No. 399-019, August 10,

1981.) N252 (Harvade®) Technical was administered in the feed at concentrations of 0, 300, 1000, or 3000 ppm and fed for one year to 6 beagle dogs/sex/group. High dose resulted directly/indirectly in mortality (1/6 males and 3/6 females)**.** Body weight and food consumption were decreased, platelet counts and the incidence of erratic heartbeat were increased for the high dose group. Some chemical chemistry value changes, gastro-enterocolitis and effects on the testis were considered a probable result of reduced nutrition. NOEL = 1000 ppm. **Possible adverse chronic effects**. ACCEPTABLE. (J. Remsen, 6/28/85).

ONCOGENICITY, RAT

No study submitted (see chronic/onco combined).

ONCOGENICITY, MOUSE

** 006, 025 986753, 051259 Serota, D. G, R. D. Alsaker, D. A. Banas and W. L. Fezio. "18-Month Toxicity and Oncogenicity Study in Mice." (Hazleton Laboratories America , Inc., Project No. 798-180, February 6, 1981.) N252 Technical (lot BL 8461), assumed to be 100% pure, was admixed with the feed at concentrations of 0, 80, 400, or 2000 ppm for 18 months and fed to 50 CD-1 mice/sex/group and evaluated for oncogenicity. Body weight was reduced during portions of the study for the high dose group. Hematocrit and hemoglobin levels were increased for mid and high dose groups. Systemic NOEL = 80 ppm. No adverse effect reported. Initially reviewed as unacceptable (analysis of feed/test article mixture not reported). Possibly upgradeable. (J. Remsen, 7/1/85). Submission of 051259 supplied the missing data on the analysis of diet, upgrading the study to ACCEPTABLE status. (Gee, 5/29/01)

REPRODUCTION, RAT

** 002 986758 MacKenzie, K. M. "Two-Generation Rat Reproduction Study with N252." (Hazleton Raltech, Inc., Study No. 79033, January 21, 1982.) N252, purity 99.7%, was admixed with the feed at concentrations of 0, 50, 200, or 800 ppm and fed to two generations of 15 male and 25 female Charles River CD (SD)BR rats/group/generation and evaluated for reproductive and developmental effects. Reduced body weight and body weight gain was reported at the high dose, especially for dams. Systemic parental NOEL = 200 ppm/day. Reproduction/developmental NOEL = 800 ppm. No adverse effects. ACCEPTABLE. (J. Remsen 6/28/85).

005 025833 Supplement to 986758.

TERATOLOGY, RAT

Summary statement: Considering the three submissions for the rat teratology study, the evaluation is that the study is still unacceptable but upgradeable with satisfactory information on the dosing material. If records of the original preparation of the test material for dosing are available, they may serve to verify the actual doses given as well as the purity. The other deficiencies have been

addressed by two supplemental submissions, records 037069 and 064078. (Gee, 6/1/01)

003 986756 Knickerbocker, M. "Teratological Evaluation of N252 (Harvade Technical) in Sprague-Dawley Rats." (Food and Drug Research Laboratories, Inc., (Waverly Research Center) Lab No. 5584, December 1, 1977.) N252 Technical (purity not stated) was administered orally via intubation and evaluated for developmental effects at concentrations of 0 (corn oil), 80, 400, and 800 mg/kg with 20 pregnant Sprague-Dawley females/group during gestation days 6 through 15. Due to excessive mortality, after 2 weeks, the 400 and 800 mg/kg groups were replaced with dose groups at 30 and 160 mg/kg. No data were provided for the 400 and 800 mg/kg dams as they were terminated early. One third of fetuses were given a visceral exam and the remaining fetuses, a skeletal exam. Aspirin was included as a positive control. NOEL = 160 mg/kg/day. Reviewed as unacceptable (lack of individual data, no purity of the test article and no analysis of dosing material). (J. Remsen, 6/28/85). See records 037069 and 060478 below for supplemental submissions.

021 037069 Resubmission of 986756. Pages 1 – 15 are exact duplicates. The remaining pages, 16 through 382, contain additional data, primarily handwritten pages for individual animals. This resubmission did not contain the other requested information regarding the test material and dosing analysis. The study remains UNACCEPTABLE but possibly upgradeable (see 1-liner 060478 below). No worksheet. (Gee, 5/25/01).

027 060478 R. A. Cardona (Uniroyal Chemical company, Inc.) sent additional data in support of the rat teratology study (986756). The information (sent on 9/1/87) includes data on individual maternal body weight, gross necropsy and fetal measurement and external examination. The author mentioned that uterine weights were not recorded and added, "…but the urogenital tract for each animal was examined in detail for anatomical normality." Test article (Technical) purity, analysis of dosing material (to confirm homogeneity, stability and content), and a section on statistical analysis were not addressed. UNACCEPTABLE but possibly upgradeable if the dosing material issue can be resolved. No worksheet. (Kishiyama and Gee, 5/30/01).

TERATOLOGY, RABBIT

025 051260 McMeekin, S. O. "Range-Finding Teratology Study in Rabbits." (International Research and Development Corporation, Report 399-027, August 21, 1981.) N252 Technical (purity not given) was administered as a single gavage per day at doses of 0 (0.5% CMC), 25, 50, 100, 200, and 400 mg/kg/day to 5 artificially inseminated Dutch Belted female rabbits on gestation days 6 through 27. Excessive mortality (100%) prevented evaluation of the 100, 200, and 400 mg/kg/day groups. Body weight was reduced slightly and body weight gain reduced occasionally for the 50 mg/kg/day dams. Litter size was reduced for 50 mg/kg/day group (2.7 versus 5.3 for control group). NOEL = 25 mg/kg/day. Supplemental (range-finding study). (Kishiyama and Gee, 5/29/01)

005 986755 Schardein, J. L., Study Director. "Teratology Study in Rabbits". (International Research and Development Corporation, study no. 399-028, July 15, 1981.) N252 (Harvade Technical, purity not stated) was administered via gavage at concentrations of 7.5, 20, or 40 mg/kg/day to 16 mated Dutch Belted rabbits/group during gestation days 6 through 27 and evaluated for developmental toxicity. Body weight decrease was marginal for the high dose group. Maternal NOEL = 20 mg/kg/day. Developmental NOEL = 40 mg/kg/day. No adverse effects reported. UNACCEPTABLE, possibly upgradeable (justification for dose selection is

needed, purity of test material, analysis of dosing solution). (J. Remsen; 6/28/85). The range-finding study, 051260, was submitted and reviewed for justification of dose selection. The doses in the main study have been justified. The remaining issue is the analysis of the dosing material for the actual doses given or adequate verification of the preparation. Possibly upgradeable. (Gee, 5/29/01)

GENE MUTATION

006 986760 Myhr, B. C. "Mutagenicity Evaluation of Harvade® (N 252) in the Mouse Lymphoma Forward Mutation Assay". (Litton Bionetics, Inc., LBI Project No. 20989, June 1981.) Harvade, purity 98%, at concentrations of 0 (DMSO), 1.56, 12.5, 25, 50, and 75 µg/ml without metabolic activation and at 0, 12.5, 50, 75, 100, and 150 µg/ml with metabolic activation (trial 1) and at 0, 25, 50, 75, 100, 150, and 200 µg/ml with metabolic activation (trial 2), was evaluated for the ability to induce mutations in mouse lymphoma cells. UNACCEPTABLE (no individual data, single trial without activation) **Harvade® was weakly mutagenic in the presence of S9 Mix.** (J. Remsen, 6/28/85).

006 986761 Jagannath, D. R. and D. Brusick. "Mutagenicity Evaluation of N 252, Technical Lot D10406, BL8998 CC0005 in the Ames *Salmonella*/Microsome Plate Test". (Litton Bionetics, Inc., LBI Project No. 20838, July 1978.) N 252, purity not stated, lot D10406, was tested at concentrations of 0 (DMSO), 1, 10, 100, 500 and 1000 µg/plate with and without metabolic activation (S9 Mix) for mutagenicity using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, one plate per concentration. UNACCEPTABLE (single plate per concentration, high concentration not justified). Not upgradeable. No mutagenic effect reported. (J. Remsen, 6/28/85).

** 006 986762 Jagannath, D. R. "Mutagenicity Evaluation of Harvade (N252) 98% D-11401 in the Ames *Salmonella*/Microsome Plate Test". (Litton Bionetics, Inc., LBI Project No. 20988, March 3, 1981.) Harvade, purity 98%, was tested at concentrations of 0 (DMSO), 1, 10, 100, 500, 1000, 2500, 5000, and 10000 µg/plate, in duplicate, with and without metabolic activation (S9 Mix) for mutagenicity using *Salmonella typhimurium* strainsTA98, TA100, TA1535, TA1537, and TA1538 with a repeat trial using strains TA98 and TA100. No evidence of mutagenicity reported. No adverse effect. ACCEPTABLE. (J. Remsen, 6/28/85).

CHROMOSOME EFFECTS

022 043276 Sorg, R. M. "CHO Metaphase Analysis *In Vitro* Chromosome Aberration Analysis in Chinese Hamster Ovary Cells (CHO)". (Pharmakon Research International, Inc., PH 320-UN-001-83, August 24, 1983.) Harvade® (purity not stated) was evaluated for mutagenicity at concentrations of 0, 5, 25, and 50 µg/ml of medium with and without metabolic activation (S9 Mix) for 5 hours followed by 6 – 8 hours and 14 – 18 hours further incubation. Chinese Hamster Ovary Cells (CHO K1-BH_4) were used in duplicate cultures. The assay was repeated. Harvade in both assays did not increase cell aberrations with or without metabolic activation. UNACCEPTABLE (test article purity and stability; no individual data). Possibly upgradeable. (Kishiyama and Gee, 5/25/01)

022 043277 Mosesso, P. "Micronucleus Test: Test Substance: Dimetipin Tech". (Life Science Research, Roma Toxicology Centre, Italy, Report No.: 131-002, November 20, 1984.)

Dimethipin Technical, purity 98.9%, was evaluated for its effect on the chromosomes of the bone marrow when administered via gavage on two successive days at concentrations of 0, 22, 73.3, and 220 mg/kg and at 0, 30, 100, and 300 mg/kg to Swiss CD-1 male and female mice, respectively. Mortality prior to scheduled sacrifice was 100% and 20% for high dose females and males, respectively. All surviving animals were sacrificed 6 hours after the second dose. Dimethipin treatment did not increase micronucleated polychromatic erythrocytes. Mitomycin C was used as the positive control and was functional. UNACCEPTABLE (bone marrow cells sampled only once). Not upgradeable. (Kishiyama and Gee, 5/29/01).

006 986759 Galloway, S. M., Study Director. "Mutagenicity Evaluation of Harvade (N 252) 98% D-11401 in the Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells." (Litton Bionetics, Inc., LBI Project No. 20990, April 1981.) Harvade, purity 98%, was tested at concentrations of 0 (DMSO), 1.56, 3.13, 6.25, 12.5, 25 and 50 µg/ml without metabolic activation and at 0, 3.1, 9.3, 27.8, 83.3, 250, and 750 µg/ml with metabolic activation and also at 0, 75, 100, 124.75, 150, and 200 µg/ml with metabolic activation for the ability to induce sister chromatid exchanges in Chinese Hamster ovary cells. No adverse effect reported. UNACCEPTABLE (unclear or lacking information on the number of replicate cultures, cells or chromosomes/cell). Possibly upgradeable. (J. Remsen, 7/1/85).

DNA DAMAGE

** 022 043278 Forster, M. A., Study Director. "Mitotic Gene Conversion in *Saccharomyces cerevisiae* D4: Test Substance: Dimetipin Tech." (Life Science Research, Roma Toxicology Centre, Italy, LSR-RTC Report No. 131001-M-00284, May 22, 1984.) Dimethipin Technical, purity 98.9%, at concentrations of 0, 125, 250, 500, 1000, and 2000 µg/ml (limit of solubility) was evaluated for the ability to induce mitotic gene conversion in *Saccharomyces cerevisiae* strain D4 at trp-5 and ade-2 loci. There were two trials with triplicate plates per concentration per trial. Dimetipin treatments, with and without metabolic activation, in both experiments did not increase conversion frequencies. Positive controls were functional. ACCEPTABLE. (Kishiyama and Gee, 5/29/01).

028 116088 Bootman, J., and D. C. Lodge. "ARS 7728: Assessment of Its Ability to Induce Genetic Damage in *Saccharomyces cerivisae.*" (Life Science Research, Lab Project ID No. 82/UR0007/408, 1982.) ARS 7728, technical grade but purity not stated, was evaluated for the ability to induce mitotic aneuploidy at concentrations ranging from 1 to 2000 µg/ml with and without metabolic activation (S9 Mix) using *Saccharomyces cerivisiae* strain D6, an adenine requiring strain and resistant to cycloheximide. One trial with triplicate plates per concentration. ARS 7728 did not induce genetic damage in *Saccharomyces cerivisiae* strain D6 under the conditions of this assay. Positive controls were functional. UNACCEPTABLE (purity not stated, triplicate plates in a single trial). Not upgradeable. (Kishiyama and Gee, 5/29/01).

NEUROTOXICTY

Not Required at This Time